

Title: NOTCH RECEPTOR LIGANDS AND USES THEREOF
Express Mail No. EL976386898US, Docket No.: 59516-159/PP-01602

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FIGURE 1

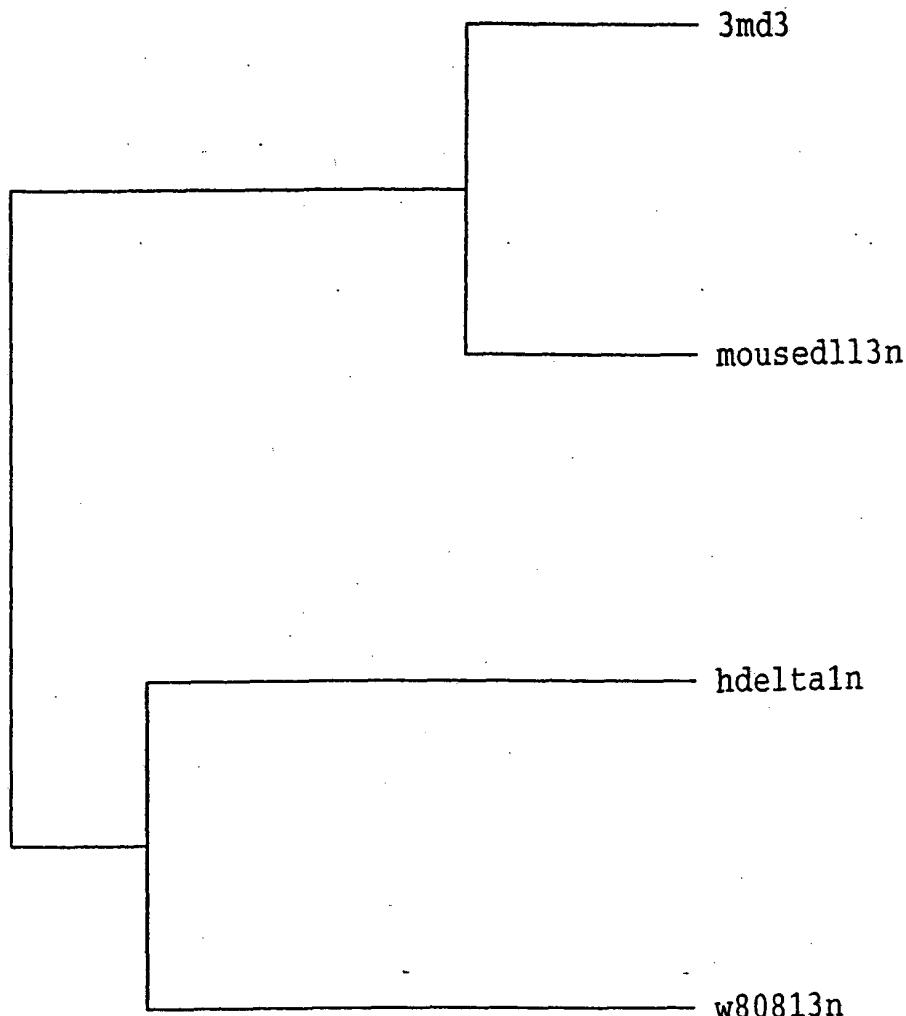


FIGURE 2

Title: NOTCH RECEPTOR LIGANDS AND USES THEREOF
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FIGURE 3A

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FIGURE 3B

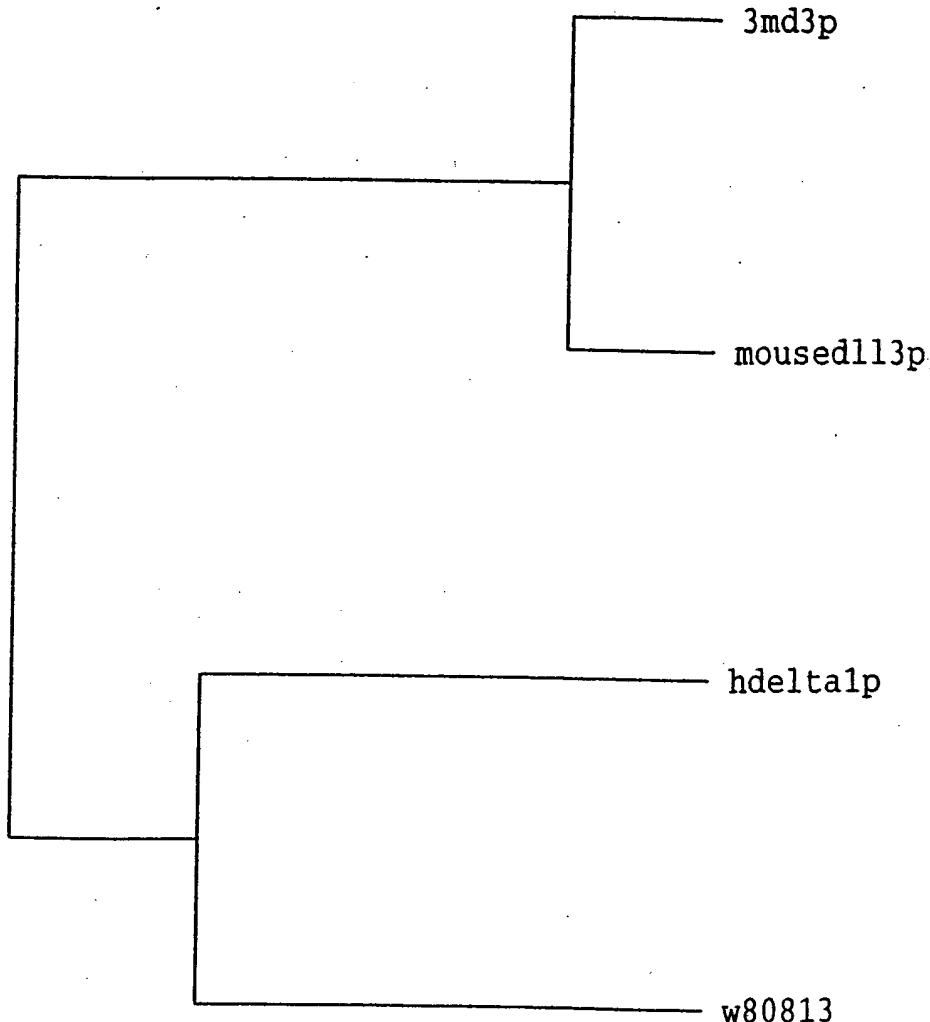


FIGURE 4

3md3 Nucleotide Sequence: 1752 (SEQ ID NO:1)

ATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCCAGACTGTGATCTAGC
GCTCATTTCTCCCCAGACACGGCCCGTGGCTTCGAGCTGCAGA
TCCACTTTCGGCCGGGTCAGGCCCTGGGCCCCCGCGGTCCCCCTGC
AGCGCCGGCTCCCTGCCCTCTTCAGACTGCCCTGAAGCTGG
GCTCTCAGAGGGCCGGCAGTCCCGTGCGCCCTGGCGCGCTGA
GTGCGCGGGACCGGCTACACCGAGCAGCCGGAGCGCCCGCCTGAT
CTCCCACTGCCCGACGGCCTCTTGCAAGGTGCCCTCCGGACGCCCTGGC
TGGCACCTCTTCTCATCGAAACCTGGAGAGAGGAGTTAGGAGACC
AGATTGGAGGGCCCGCTGGAGCCTGCTGGCGCGGTGGCTGGCAGCGG
CGCTTGGCAGCGGAGGCCGTGGGCCGGGACATTCAAGCGCGCAGCGC
CTGGGAGCTGCGCTGCTCGTACCGCGCGCTGCGAGCGCCCTGCGGTG
GGACCGCGTGCACGCCCTCTGCCGTCCCGCAGCGCCCTCGCGGTG
GGTCCGGACTGCCCTCGCGCACCGCTCGAGGACGAATCGGTGTGCCG
AGCAGGCTGCAGCCCTGAGCATGGCTTCTGTAACAGCCGGTGAATGCC
GATGCCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACC
AGCAGCTGCCCTAGCCCCAGGGGCCGTCCCTGCTACCAACCGGATGCC
TGTCCCTGGGCTGGGCGTGTGACGGGAACCGTGTGCCAATGGAGGCA
GCTGTAGTGAGACACCCAGGTCTTGAAATGCACCTGCCCGCGTGGGTC
TACGGGCTGCGGTGTGAGGTGAGCGGGGTGACATGTGCAAGATGGACCTG
CTTCAACGGCGGCTTGTGTGTCGGGGGTGAGACCCCTGACTCTGCCCTACA
TCTGCCACTGCCAACCTGGTTCCAAGGCTCAAATGTGAGAAGAGGGT
GACGGGTGCAGCCTGCAGCCATGCCGCAATGGCGACTCTGCCCTGGACCT
GGGCCACGCCCTGCGCTGCCGCTGCCGCGGCCCTCGCGGGCTCGCT
GCGAGCACCTGGACACTGCGCGGGCCGCCTCGCGCTAACGGCGC
ACGTGTGTGGAGGGCGCGCGCAGCCGCTGCTCTGCCGCGTGGGCTT
CGGCCGCGCGACTGCCGCGAGCGCGCGGACCCGTGCCGCCGCCCT
GTGCTCACGGCGCCGCTGCTACGCCACTTCTCCGGCTCGTCTGCGCT
TGCCTCCCGCTACATGGGAGCGCGGGTGTGAGTCCCAGTGCACCCGA
CGGCCAACGCCCTGGCCGGCCCCCGCCGGCTCAGGCCGGGACC
CTCACGCCCTACCTTTGCCCTCCGGCTCGGACTGCTCGTGGCCGGG
GTGGCCGGCGCTGCCCTTGCTGGTCCACGTGCGCCGCCGTGGCACTC
CCAGGATGCTGGGCTCGCTTGCTGGCTGGGACCCCGAGCCGTAGTCC
ACGCACCTCCGGATGCACTCAACAACCTAACGGACGCAGGAGGGTTCCGG
GATGGTCCGAGCTCGTCCGTAGATTGGAATGCCCTGAAGATGTAGACCC
TCAAGGGATTATGTATCTGCTCCTCCATCTACGCTCGGGAGGCCT
GA

FIGURE 5A

3md3 Protein Sequence: 583 (SEQ ID NO:2)

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGAPRSPCS
ARLPCRLFFRVCLKPGLSEAAESPCALGAALSARGPVYTEQPGAPAPDLP
LPDGLLQVPFRDAWPGTFSIIETWREELGDQIGGPAWSLLARVAGRRLA
AGGPWARDIQRAGAWELRCSYRARCEPPAVGTACTRLCRPRSAPSRCGPGL
RPCAPLEDESVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLS
PRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFEETCPRGFYGLRCE
VSGVTCADGPCFNGGLCVGGADPDSAYICHCPGFQGSNCEKRVDRCSLQP
CRNGLCSDLGHALRCRAGFAGPRCEHDLCAGRACANGGTCVEGGGA
HRCSCALGFGRDCRERADPCAARPCAHHGRCYAHFSLVCACAPGYMGAR
CEFPVHPDGASALPAAPPGLRPQDPQRYLLPPALGLLVAAGVAGAALLVH
VRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSVDWNR
PEDVDPQGIYVISAPSIYAREA

FIGURE 5B

FIGURE 6

2hd1 nucleotide sequence (SEQ ID NO:3)

AGTACTCCTACCGCTTCGTGTGACGAACACTACTACGGAGAGGGCTGCTCCGTTTCT
GCCGTCCCCGGGACGATGCCCTCGGCCACTTCACCTGTGGGAGCGTGAGAAAGTGT
GCACCCCTGGCTGAAAGGCCCTACTGCACAGACCGCAGGGACGGGCTTCTGAGCCACGGG
GGCTCACTCGTCCACGAACACGGACCACGGCAGGGACGGGCTTCTGAGCCACGGG
GCTGGGACTGTAGAGATGTTCTGGGGAAACTGAGGCCAGAGGACAGAAGTGGATT
GCTATAAGTCACGCTCGTCAGTGAGGGGGTTGGGTCAACGCAGACATTAACTCCC
AGGCTGTGTTATCCACTATCGGAACGTGCTTCTTAATCAGGGAGGATTAGAGACAG
GGCCAGGGGTCAAGGAAGTAAAGCCAGTGTACCCCCARGGTGTGTATTAGAGAGGGAG
AGGAGGAAGGAAGGGAGGAACACAGAGAGCTTGTTGTCAAGGGCACCATTTAACCC
GAGTTCCCACTGCTGGAACAGCATCACACTGGAAACGTTCCATTTCCTCTGGAGCTG
GTGTGCTTGACCTCTGGAGCAAACGCCCTTCCGGATACTCCCTGTGACACGCCACTGTC
TATGCTGGCCAGAGAGCAGGCTTCACTCCTGTGGGCTGTGAGGCCAGGTCTCAAGC
CTGTGTGGGCAGGGGTGCAAGCCCGTCTGGCTTGAATGCTCAGGCACACCTGCT
GGAAAAGCAATGTCATGGCAGGCAAGGTACTAGGGCAGGGTGGGGCCGTGCTGGCTCCTGG
TGTGTCAATGTCATGGCAGGCAAGGTACTAGGGCAGGGTGGGGCCGTGCTGGCTCCTGG
TTCTGGCTCATGGGACCTCAGGAGCCCTCTCCAGCTGACTGAGGCCCTGGCTGACG
CCTGGCCCGTCCAGCCATTGGTACCGGATTCTACAGCTGGGATGGGTAGGTC
TGGAGCTGCCAGAAAACTCCAGGGAACTGTCATTCTCCCTGGAACTGGACAACCTT
GGAGAGGGGCTCTGGAGGCCAGAACCTCTGGCAGGAGCTGGTAGTGCCTGGGTGA
GGGTGGGTCTTCCATTCACTGAGTCCTGATGCTTGCCTTAGCTTCCAAATTC
CCTCCGGAACTTACTGAGCTCTTCAAGCTTGCTTGCCTGAACTGGTTCTGGGAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

2hd1 protein sequence (SEQ ID NO:4)

GRTDLKYSYRVCDEHYGEGLSVFCRPRDDAFGHFTCGERGEKVCNPWKGPYCTERES
LGRHRWLTRPRTTRRDGAS

Notch signalling

FIGURE 7

Upon binding to Delta or Jagged (Notch ligands), the intracellular domain of Notch is cleaved by a presenilin-dependent pathway and translocates to the nucleus along with DNA-binding protein, CSL, to activate transcription of downstream genes. The intracellular domain of Notch also downregulates the JNK pathway through a CSL independent mechanism. Modulators of the pathway include Kuzbanian, an ADAM protease that positively regulate Notch signalling, and Fringe, a putative glycosyltransferase that inhibits Jagged signalling.

